REMARKS

The Office Action dated January 11, 2006, has been received and reviewed. Claims 52-54, 57-67, 70-75 and 85-91 are pending in this application. Claims 55, 56, 68, 69 and 76-84 have been canceled without prejudice or disclaimer and only have been canceled to expedite prosecution of the pending set of claims. Applicants reserve the right to file any canceled subject matter in one or more continuing applications. Claims 85-91 have been added. Independent claims 52 and 64 and dependent claims 53, 54, 61, 62, 65-67 and 70 have been amended to more distinctly claim the invention. Claims 52-84 were rejected in this Office Action and these rejections will now be argued as they apply to pending claims 52-54, 57-67, 70-75 and 85-91. Applicants respectfully request reconsideration of the claims as amended herein and in view of the remarks below. Applicants further request reconsider of Dr. Adler's previously submitted declaration and a new declaration by Dr. Duncan Rogers, author of one of the publications relied upon by the Examiner in support of his lack of enablement rejection.

I. Claim Amendments

Independent claims 52 and 64 have been amended to recite "A method of inhibiting the MARCKS protein-related release of an inflammatory mediator." The phrase "MARCKS protein-related" has support throughout the specification and in the original claims as filed. It is clear from the specification, for example, such as in paragraphs [0015] and [0016] that MARCKS is a protein and from paragraphs [0017] and [0018] of the specification and original claims 24 and 31 that the release of inflammatory mediators is MARCKS protein-related. These claim amendments more specifically define applicants' invention. Claims 53 and 66 are amended to clarify that the inflammation can be cause by a respiratory disease. Claims 54 and 67 are amended to only refer to asthma as the cause for inflammation. Claim 61 is amended to make it clear that the mediators are released from the inflammatory cells and is supported in paragraph [0009] and throughout the specification. Claim 62 is amended to include the nasal route and is supported in original claims 10 and 22 and in paragraph [0016]. Claim 65 is amended to include the same phrase as claim 64 that is "MARCKS protein-related." Claim 70 is amended to correct a minor typographical error to reference back to the inflammatory cell in claim 64. New claims 85, 86, 88 and 89 separately claim the diseases from claims 54 and 67, each of which are amended accordingly. The abbreviation

"COPD" has been replaced with the complete name "chronic obstructive pulmonary disease" which is the known complete name for COPD. COPD is found throughout the specification and chronic obstructive pulmonary disease is found in paragraph [0011]. Claims 87 and 90 have support in paragraph [0011] as an airway disease and in original claim 7. Claim 91 contains similar language to claim 62 and is further supported by paragraph [0016]. The claims have been amended to clearly define the present invention and to expedite prosecution..

II. New Matter Rejections – 35 U.S.C. § 112, First paragraph

Claims 55, 56, 64-75 and 76-84 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner describes this rejection as a new matter rejection and states that specific phrases represent a departure from the specification and claims as originally filed. Applicants respectfully disagree with the Examiner's position and maintain that the specification and claims as originally filed do support the presently pending claims.

As stated in the last response, the phrase, "a membrane-bound vesicle in an infiltrating inflammatory cell in a subject" in claim 64 is supported by the abstract and paragraphs [006], [0015], [0039], [0040], [0047] and [0081] of the specification as filed. All of these portions of the specification support that the inflammatory mediator is released from membrane-bound vesicles. The first sentence in paragraph [0081] recites: "The invention also relates to a new method for blocking any cellular secretory process, especially those releasing inflammatory mediators from inflammatory cells, whose stimulatory pathways involve the protein kinase C (PKC) substrate MARCKS protein and release of contents from membrane-bound vesicles." Then, data are provided showing the release of myeloperoxidase from neutrophils, with reference to the results in FIGS 9 and 10, followed by the sentence, beginning on line 16, that recites: "Thus, the peptide may be used therapeutically to block the release of mediators of inflammation secreted from **infiltrating inflammatory cells** in any tissues." Reading paragraph [0081] as a whole, it is clear that the inflammatory cells contain membrane-bound vesicles that release the inflammatory mediators and these inflammatory

cells infiltrate into tissue at the site of inflammation. Additionally, it is well known to immunologists that during the inflammation process, inflammatory cells infiltrate to the inflammation site, and it is these infiltrating cells that contain the membrane-bound vesicles that contain and release the inflammatory mediators. See for example, Immunology, Roitt *et al.*, (1985), (Attachment A), particularly page 1.3, bottom of right column, which explains inflammation as including the migration of leucocytes, particularly neutrophil polymorphs and pages 2.12 and 2.13 show the different types of polymorphonuclear granulocytes (polymophs) that include neutrophils, eosinophils, and basophils that all contain granules containing inflammatory mediators. Applicants submit that paragraph [0081] and the other identified portions of the application as filed, provide support for the phrase in claim 64. The Examiner is requested to withdraw this rejection in regard to this phrase based upon this further explanation and further identified support.

In regard to the phrase "provoked by said inflammatory mediator in a subject" in claims 55, 68, and 76, and the phrase "wherein said inflammatory mediator results in inflammation caused by inflammatory airway diseases" in claims 56, 69, and 77, each of these claims have been canceled and these rejections are now moot.

III. Claims Rejections – 35 U.S.C. § 112, First paragraph

Claims 52-84 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention and as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner states that the independent claims 52, 64 and 76 are not enabled because the specification fails to provide empirical data to show that the method would work *in vivo*. At issue, the Examiner states are whether (1) the claimed methods will work *in vivo*, (2) the claimed method would inhibit any inflammatory mediator release, (3) the claimed method would inhibit the release of an inflammatory mediator from membrane bound vesicles in infiltrating cells, or (4) the claimed method would inhibit the release of an inflammatory mediator and mucus secretion provoked by the inflammatory mediator.

Applicants respectfully traverse these rejections and request reconsideration based on the presently pending set of claims and for the reasons enumerated below.

A. Issue 1

In regard to issue 1, applicants do not understand the Examiner's rationale for discussing the state of the art in treating only airway mucus hypersecretion and utilizing the Rogers 2003 and Barnes 2002 publications. Even more confusing are the Examiner's comments that the specification relies upon inhibiting mucin secretion by the MANS peptide as an assay to determine MANS peptide activity and the specification discloses no efficacy. In response to the issues raised by the Examiner, applicants herewith provide a declaration under 37 C.F.R. § 1.132 made by Dr. Duncan Rogers (See Attachment B), the author of one of the publications cited by the Examiner and a colleague of Dr. Barnes. Dr. Rogers read the Office Action of January 11, 2006, and the Examiner's arguments that are allegedly supported by his and Dr. Barnes' publications, and on that basis provides his declaration. It is requested that the Examiner review this enclosed declaration and consider its content in support of applicants' position.

Briefly, in paragraph 2 of his declaration, Dr. Rogers questions the relevance of the Examiner's use of his 2003 and Dr. Barnes 2002 publications in support of the lack of enablement rejection in regard to whether the claimed method would work *in vivo*. Based on his understanding that the present invention is directed to inhibiting the MARCKS-related release of an inflammatory mediator and his knowledge in the field of respiratory physiology that mucus hypersecretion does not cause inflammation of the airways, he does not find the publications cited by the Examiner to be relevant to determine whether the claimed invention is enabled. However, Dr. Rogers does address the Examiner's basis for lack of enablement to maintain normal mucus secretion while inhibiting mucus hypersecretion. In this regard, Dr. Rogers states that one skilled in the art would be able to determine this level of inhibition of mucus hypersecretion without undue experimentation during clinical trials, and adjust the dosage accordingly.

Further in paragraph 3 of Dr. Rogers' declaration, he views the inhibition of airway mucus hypersecretion as a valid therapeutic target in both COPD and asthma, and particularly views anti-MARCKS therapy as a logical approach to reducing airway mucus hypersecretion. Along this same line of reasoning, Dr. Rogers than notes that the Barnes 2002 publication

cited by the Examiner also identified MARCKS inhibitors as potential treatment for the airway mucus hypersecretion in COPD. Dr. Rogers further notes that his own 2003 publication cited by the Examiner, his 2004 publication (Exhibit 2) and Dr. Barnes 2002 publication cited by the Examiner, all cite Li *et al.* (Exhibit 3) which is a publication by the present inventors as evidence that anti-MARCKS therapy to inhibit airway mucus hypersecretion merits consideration for treatment. Similarly a subsequent publication by Dr. Adler's group, Singer *et al.* (Exhibit 4) extends this work and shows that MANS peptide inhibits mucus secretion in the mouse model of asthma which confirms that Drs. Rogers and Barnes were correct in supporting the role of anti-MARCKS therapy as a viable treatment to inhibit airway mucus hypersecretion. Although, applicants provide Dr. Rogers' comments in response to the Examiner's use of his and Dr. Barnes' publications, it is clear from Dr. Rogers' declaration that he does not consider that mucus secretion can cause inflammation, and thus he does not consider the Examiner's reliance on his and Dr. Barnes publications to be relevant to the claimed invention.

Additionally, applicants would like to direct the Examiner's attention to Nguyen *et al.* (Attachment C) which provide an example in which the *in vivo* activity related to a myeloperoxidase-dependent pathway can be predicted by an *in vitro* myeloperoxidase assay. The present application provides two examples with data shown in Figures 9 and 10 of *in vitro* assays that show that the MANS peptide inhibits the release of myeloperoxidase. Applicants submit that additional *in vitro* examples of other inflammatory enzymes that also are inhibited by the MANS peptide are provided in Takashi *et al.* (Attachment D). This publication provides evidence of *in vitro* assays showing that MANS peptide inhibits the release of inflammatory mediators from different inflammatory cells, and Nguyen *et al.* provide evidence that *in vitro* assays are predictive of *in vivo* activity.

Therefore, in view of the favorable declaration that is supportive of applicants' invention from Dr. Rogers, the author of one of the publications cited as a supporting publication by the Examiner, it is requested that the Examiner consider Dr. Rogers' declaration and it supporting exhibits as well as the Nguyen *et al.* as providing sufficient support that the claimed methods would work *in vivo*. In view of this information and supporting arguments, it is requested that the Examiner withdraw the rejections on the grounds of lack of enablement.

B. Issues 2 and 3

In response to the Examiner's lack of enablement rejection, and particularly with respect to issues 2 and 3, raised by the Examiner, applicants also submit a copy of a manuscript by Takashi *et al.* (Attachment D). Dr. Adler, one of the inventors of the present application, is one of the authors of this publication. This publication shows that the release of inflammatory mediators other than myeloperoxidase can be inhibited or attenuated by the MANS peptide. For example, the data show that degranulation or the release of inflammatory mediators from inflammatory cells is inhibited by the incubation of these different cells with the MANS peptide. The data in this publication utilized four different types of leukocytes to study the role of MANS peptide in the release of inflammatory mediators. Specifically, in addition to isolated human neutrophils, cell lines representative of human eosinophils, monocytes/macrophages and lymphocytes were assayed to determine if there was any response to stimulated degranulation. These cells were selected for study because in addition to myeloperoxidase, inflammatory mediators, such as eosinophil peroxidase (EPO) and major basic protein (MBP) are present in and are released by eosinophils, lysozyme in monocytes/macrophages and granzyme in natural killer (NK) cells and cytotoxic lymphocytes. It is known by persons skilled in the art that these mediators are released at sites of injury and contribute to inflammation and repair in the lungs and in other tissues. Further, it is requested that the Examiner take this data into consideration regarding the comment that he makes on page 5 of the January 11, 2006 office action, where he states that "the specification provides no evidence that the claimed basophils, eosinophils, monocytes or leukocytes would respond to the MANS peptide and inhibit the release of any inflammatory mediators in the same manner as the activated neutrophils ...." Applicants submit that the Takashi publication provides this information, and should satisfy the Examiner's concern. This data show that the claimed methods do inhibit the release of several different inflammatory mediators, and applicants submit that this data are sufficient to overcome the bases which the Examiner has raised as supportive of his alleged lack of enablement rejection.

Additionally this data show that the MANS peptide does inhibit the release of an inflammatory mediator from infiltrating cells. Applicants submit that it is known to persons skilled in the art that leukocytes are the cells that infiltrate sites of inflammation and are

responsible for the recognizable symptoms of inflammation. The Takashi publication provides representative examples of such infiltrating inflammatory cells and shows that the MANS peptide inhibits the release of inflammatory mediators from these cells. In view of this additional information, applicants submit that this data are sufficient to overcome this issue raised by the Examiner as supportive of his alleged lack of enablement rejection.

In response to the Examiner's misguided statement that "the specification fails to demonstrate that all these inflammatory mediators are carried by the same membrane-bound vesicle in an infiltrating inflammatory cell, so that the release of one indicates a release of all at the same time", applicants wish to explain the science of the contents of inflammatory cells. Different types of inflammatory cells contain different type of granules, each of which contain different mediators. For example, individual granules in leukocytes do not contain multiple mediators, but in fact, the leukocytes, as well as other types of inflammatory cells, contain multiple types of granules which each contain different mediators. Individual granules do not contain more than a single mediator. The data provided in the Takashi publication tested the effects on only one mediator per cell, and tested the effect of the MANS peptide on the release of the major mediator for each cell type tested. The Takashi data show that release of the major inflammatory mediators of each cell type were inhibited by MANS peptide. Therefore, applicant submit that the specification does not need to demonstrate that all these inflammatory mediators are carried by the same membrane-bound vesicle because, in fact, the vesicles each contain different mediators.

C. Issue 4

In response to the Examiner's lack of enablement rejection, and particularly with respect to issue 4, applicants believe that this basis for rejecting the claims on lack of enablement is now moot because previous claim 76 has been canceled, and this basis for rejection is no longer a viable grounds for the alleged lack of enablement rejection.

D. Reconsideration of Dr. Kenneth Adler's Declaration

Applicants further submit that neutrophils are recognized as being correlated to inflammation and applicants request that the Examiner again refer to Dr. Kenneth Adler's declaration, attached as Appendix A to the previous response, and particularly refer to paragraphs 6–9, in which Dr. Adler discusses how *in vitro* studies with granulocytes, which includes neutrophils and eosinophils, are predictive of the outcome of inflammatory diseases

in vivo. In paragraphs 8 and 9 of his declaration, Dr. Adler provides two publications where granulocytes are used in *in vitro* studies and relied upon as predictive of *in vivo* outcome by the authors. Applicants submit that these publications are indicative that one skilled in the art would accept the *in vitro* model of studying stimulated neutrophils as reasonably correlated to inhibiting the release of an inflammatory mediator in a subject. As previously argued, "[a] rigorous or an invariable exact correlation is not required." (MPEP § 2164.02, page 2100-188, first column). Applicants note that if the art is such that a particular model is recognized as correlative to a specific condition, then it should be accepted as correlative unless there is evidence that the model does not correlate. *See*, M.P.E.P. § 2164.02; *See also, In re Brana* 51 F.3d 1560, 1566. Therefore, Applicants submit that Dr. Adler's comments and the supporting publications provide evidence that the enablement standard is satisfied in the present application because the *in vitro* experiments do provide evidence that are predictable and relied upon by skilled persons that can be reliably extrapolated to the behavior of these cells *in vivo*.

Specifically, the Examiner states that Haile *et al.* ("Haile") is not analogous to the issue at hand and is irrelevant to the claimed invention. However, applicants submit that this publication is supportive of applicants' position re mucus hypersecretion vis-a-vis inflammation. Thus, Haile was cited by applicants only as an example supportive of their arguments. In Haile, the authors used the drug vinblastine only as a means of inhibiting recruitment of granulocytes to the lung in this model of allergic inflammation. Vinblastine, as described on page 893, last paragraph in the second column before the heading, "Statistics" of Haile, was used as a means for inhibiting granulocyte infiltration, and as described on page 897, second column, last paragraph before the heading "Discussion," indeed successfully blocked recruitment of eosinophils, IGE-bearing neutrophils and other neutrophils to the lung. Vinblastine is known to act as a microtubule inhibitor in other systems, but its exact mechanism of action here is not known, as described by the authors on page 900, second paragraph, second column. However, the point that applicants wish to emphasize, when referring to this publication, is that the authors showed that, even in the absence of inflammation in these airways, there was still mucus hypersecretion. In addition, the presence of mucus hypersecretion did not cause inflammation, as there was no recruitment of inflammatory cells in the animals treated with vinblastine, which also showed mucus

hypersecretion. Thus, as stated by the authors of Haile, in the last paragraph on page 900, "[m]ucus hypersecretion ... was not affected even when eosinophil, IgE-bearing PMN and neutrophil recruitment was abrogated by vinblastine treatment."

Also, with regard to the lysis of eosinophils being more important than degranulation, as stated by the Examiner as quoting Haile on page 899, midway through the paragraph bridging the first and second columns which attributes this statement to a cited publication by Persson and Erjefalt (26). Applicants fail to see how this observation would make it unpredictable as to whether MANS peptide would be effective *in vivo*. Applicants submit that it is well known to persons skilled in the art that dying cells release their contents. The release of the contents from eosinophils, in no way affects other granulocytes, such as neutrophils, and the study of inflammatory mediators released from individual granules in these cells. Therefore, applicants submit that this observation by Haile does not have an impact on the predictability as to whether MANS peptide would inhibit the release of inflammatory mediators *in vivo*.

As further support to applicants' position that mucus secretion does not cause or contribute to inflammation, it is well known to clinicians and researchers in the relevant field that bronchiectasis and severe bronchitis are characterized by a loss of epithelium, so there are no mucus-producing cells present, yet these airway diseases are characterized by severe inflammation in the absence of mucus or mucus secretion.

Applicants further submit that the Examiner has misinterpreted Dr. Adler's comments with regard to the supporting documents to show *in vitro/in vivo* correlations. Applicants submit that Abdel-Latif *et al.* and Lacy *et al.* (Exhibits 3 and 4 to Dr. Adler's declaration) were provided to show that *in vitro* cells are good predictive models for what occurs *in vivo*. Applicants submit that these publications show that alterations that are known to be in effect *in vivo* are retained when the cells are removed and cultured, and are therefore relevant to support applicants' position that their specification is enabling. Accordingly, Applicants respectively request reconsideration based upon the above arguments, the arguments provided in the previous response, all of the supporting documents and the pending set of claims, and request withdrawal of the rejections to the pending claims.

IV. Claims Rejections – 35 U.S.C. § 103(a)

A. Adler et al (CHEST. May, 2000)

Claims 52-62, 64-74 and 76-83 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Adler et al (CHEST. May, 2000), (hereinafter "the Adler abstract"). Applicants traverse this rejection for the reasons set forth below, and those provided in Dr. Rogers' declaration, attached herewith, (Attachment B), and those previously provided in Dr. Adler's declaration, previously submitted (Appendix A) in regard to the presently pending claims 52-54, 57-67, 70-75 and 85-91.

To reiterate our previous arguments, to establish a prima facie case of obviousness, the prior art reference or references when combined must teach or suggest *all* the recitations of the claim, and there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. M.P.E.P. § 2143. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. M.P.E.P. § 2143.01, citing *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). To support combining references, evidence of a suggestion, teaching, or motivation to combine must be clear and particular, and this requirement for clear and particular evidence is not met by broad and conclusory statements about the teachings of references. *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). The Court of Appeals for the Federal Circuit has also stated that, to support combining or modifying references, there must be particular evidence from the prior art as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed. *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). Furthermore, as recently affirmed by the Court of Appeals for the Federal Circuit in *In re Sang-su Lee*, a factual question of motivation is material to patentability, and cannot be resolved on subjective belief and unknown authority. *See In re Sang-su Lee*, 277 F.3d 1338 (Fed. Cir. 2002). Respectfully, as was previously argued and which will be discussed below, the Official Action fails to meet the requirements for a prima facie showing of obviousness under 35 U.S.C. § 103.

As pointed out in the previous response, the Examiner is erroneously relying on the first sentence of the Adler abstract for motivation to support his position that the claims are

obvious over the Adler abstract. Applicants respectfully submit that the sentence "[h]persecretion of mucus contributes to airway inflammation and obstruction in COPD" was not intended to establish a causal link that mucus hypersecretion causes inflammation. In regard to the contents of Dr. Adler declaration that was previously submitted, the Examiner raises the issue that Dr. Adler is a concerned party but who better, indeed to explain the first sentence of his own publication, than the author. However, in another effort to convince the Examiner that mucus hypersecretion does not cause inflammation, applicants request that the Examiner review paragraph 4 of Dr. Duncan Rogers' declaration submitted herewith as Attachment B. Dr. Rogers states that the first sentence in the Adler abstract does not suggest to him that inhibition of mucus hypersecretion will inhibit inflammation in the airways because mucus hypersecretion does not have a direct effect on inflammation. Further, Dr. Rogers states that although inflammation and a myriad of inflammatory and immune mediators could affect mucus production and possibly secretion, interpreting this sentence as claiming that mucus can cause inflammation, or even suggesting that mucus can directly cause inflammation is absolutely incorrect. He further states that there is no scientific basis for such an assertion. Dr. Rogers further states that a publication by Fischer and Voynow from CHEST 2000; 117:317-320S, cited as Exhibit 5 of his declaration, suggests that an inflammation mechanism can produce mucin hypersecretion (the mechanisms are related in this cause and effect direction), but does not demonstrate or even suggest the reverse dependency.

It further should be noted that Dr. Rogers points out that one skilled in the art would realize that inflammation can occur in essentially every tissue and organ in the body, the majority of which do not produce or secrete mucus, and inhibition of release of inflammatory mediators by inflammatory cells via administration of a MARCKS-related peptide in these tissues clearly has no relationship to mucus in any sense. As Dr. Rogers' publication has been used by the Examiner to support his arguments, it is believed that the Examiner should find Dr. Rogers to be a qualified expert in the relevant field. Accordingly, the Examiner should find persuasive Dr. Rogers' statement that he would not be motivated by the CHEST abstract to administer the MANS peptide to inhibit MARCKS-related release of inflammatory peptides.

More specifically, Adler et al., CHEST 2000; 117:2266S-267S, sentence-wise recites that "[H]hypersecretion of mucus contributes to airway inflammation and obstruction in COPD"; that "...**common signaling pathways and intracellular molecules involved in mucin secretion have not been elucidated**" (emphasis added); that "...MARCKS protein ... is a central, convergent intracellular molecule controlling release of mucin granules by airway goblet cells"; that "the mechanism appears to involve secretagogue-stimulated activation of protein kinase C, which leads to MARCKS phosphorylation and detachment from plasma membrane into the cytosol ... followed by activation of cyclic guanosine monophosphate- (cGMP-) dependent protein kinases, which in turn activate a cytosolic phosphatase, dephosphorylating MARCKS and **allowing it to attach to mucin granule membranes whereby it mediates granule release via interactions with cytoskeletal components**." (emphasis added) Furthermore, the abstract recites that the authors "have identified, for the first time, MARCKS messenger RNA (mRNA) and [MARCKS] protein in human bronchial epithelial cells, and both mRNA and protein levels increased with secretory cell differentiation when these cells were maintained in air/liquid interface culture"; that "MARCKS in these cells was phosphorylated by the phorbol ester, PMA, while subsequent addition of cGMP activator, 8-bromo-cGMP, caused dephosphorylation"; that "Mucin hypersecretion provoked by the pathophysiologically relevant secretagogue, uridine triposphate, or by a combination of PMA and 8-bromo—cGMP, was inhibited in a concentration-dependent manner by a synthetic peptide with a sequence identical to the myristic acid containing N-terminal region of the MARCKS protein, the **site of its attachment to [mucin (vide supra)] granule membranes**". (emphasis added)

There is no disclosure in Adler et al. that dephosphorylated MARCKS which attaches to mucin granule membranes will also attach to any part of an inflammatory cell, nor is there any information provided that points to the novel concept of MARCKS attaching to an inflammatory cell; nor is there any disclosure that dephosphorylated MARCKS mediates granule release in an inflammatory cell; nor is there any information provided that points to the novel concept that dephosphorylated MARCKS would mediate granule release in an inflammatory cell; nor is there any disclosure of the novel concept that a synthetic peptide with a sequence identical to the myristic acid containing N-terminal region of the MARCKS protein would inhibit release of any entity in or on or from an inflammatory cell; nor is there

any information provided that points to the novel concept of a synthetic peptide with a sequence identical to the myristic acid containing N-terminal region of the MARCKS protein inhibiting release of any entity in or on or from an inflammatory cell. These novel concepts form the essence of discovery that lead to the current invention as now more clearly claimed in the amended claims. The separate biological functions of inflammatory cells and of mucin goblet cells suggest to one skilled in the art at the time the application was filed that separate mechanisms of biological action should apply rather than a common mechanism to link the diverse function of these two classes of cells. Indeed, as taught by Adler even for mucin cells, common signaling pathways and intracellular molecules involved in mucin secretion had not yet been elucidated, let alone common signaling pathways and intracellular molecules involved in both inflammation mechanisms and mucin release. The presence of two different cell types within a subject, one of which is migratory, with the two cell types having two separate and different biological functions is not sufficient to suggest to one skilled in the art that a common mechanism or common mediator would interact with each cell type. Only in retrospective analysis in view of the disclosure of the current invention is such a connection possible.

Applicants submit that the Examiner's interpretation of Adler's CHEST abstract is that it would be obvious to anyone with a knowledge in the field that the myristic acid containing N-terminal region of the MARCKS protein also would block release of inflammatory mediators. Applicants submit that this is simply not the case, and that it would not be obvious or even presumptive to think that, and that, unless the entire mechanism was understood, one skilled in the art would assume that these processes would not be similar.

Applicants wish to point out that excess mucus does not cause infection or inflammation but rather under certain conditions it may contribute to an environment for microbial growth which could result in inflammation. Microbial infection can occur by entry of a microbe from an external source, such as a microbial contaminant present in the air that is breathed in, and the infection could be bacterial, viral or fungal. Applicants submit that inhibiting mucus cannot protect a subject from these infectious agents. For example, even a normal lung without excessive mucus can be vulnerable to infections from external sources containing these infectious agents, and therefore, to inflammation. Again, applicants reiterate that mucus hypersecretion does not cause inflammation.

Again to reiterate Dr Rogers' statements and our previously presented arguments, the Adler abstract presents a study of the mechanism whereby mucus hypersecretion is inhibited by a synthetic peptide identical to the myristoylated N-terminal region of the MARCKS protein. There is no mention of the effect of this peptide on inflammation in the airway. Further, there is no information regarding how the MANS peptide would inhibit the release of any inflammatory mediators. Additionally, the first sentence of the abstract states that mucus hypersecretion **contributes** to airway inflammation but there is no information on a mechanism whereby these two conditions are related that would lead a skilled person to believe that treatment with the N-terminal region of the MARCKS protein would affect inflammation. Therefore, a person skilled in the art, such as Dr. Rogers, would not be motivated by this abstract, to inhibit MARCKS-related release of inflammatory peptides, by administering the MANS peptide.

The claims are directed to a method of inhibiting the MARCKS-related release of inflammatory inhibitors, and the CHEST publication does not disclose or suggest such a method to a skilled person. As applicants previously argued, the Adler abstract is not enabling to a person skilled in the art because it does not disclose that a skilled person can inhibit the MARCKS-related release of inflammatory mediators from inflammatory cells by administering the MANS peptide. Clearly there are no examples or statements of such a study or an experiment in the Adler abstract. Thus, the Adler abstract should also not be considered to be enabled because it does not contain any examples for inhibiting the MARCKS-related release of an inflammatory mediator. There is nothing in this abstract, which would render the present invention obvious. Applicants submit that this reference fails to contain any motivation to suggest the presently claimed invention as required by *In re Sang-su Lee*. Furthermore, even if Adler was combined with another publication, one would not arrive at the present invention as it relates to inflammatory mediators. Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection to all of the pending claims because the Adler abstract does not render the claimed invention obvious.

B. U.S. Patent No. 6,506,779

Claims 63, 75 and 84 also was rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 6,506,779 ("the '779 patent) in view of the Adler abstract. Applicants submit that the '779

patent relates to acetylene derivatives, methods of treatment and pharmaceutical compositions for the treatment of cyclooxygenase mediated diseases. It does not in any way discuss or even contemplate the MANS peptide or a MARCKS related protein. Accordingly, for the reasons stated above and in this section, and previously submitted in the last response, applicants submit that the '779 patent and the Adler abstract either alone or in combination fail to contain any motivation to combine their teachings as required by *In re Sang-su Lee*. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection to present claims 63 and 75. Claim 84 has been canceled, and therefore this rejection as applied by the Examiner to claim 84 is now moot.

V. Rejections based on Provisional Obviousness-type Double Patenting

A. Claims 52-62, 64-74 and 76-83

Claims 52-62, 64-74 and 76-83 are rejected on the grounds of nonstatutory obviousness-type double patenting as be unpatentable over claims 77-79, 82-87, 89, 90, 95, 96, 98-103, 105 and 106 of copending US. Serial No. 09/914,020 ("the '020 application). The Examiner states that although the conflicting claims are not identical, they are not patentably distinct because both sets of identified claims are drawn to the treatment of the same patient populations with the same compositions to achieve the same therapeutic effect. The Examiner further states that the basis for this rejection is that "both epithelial cells and inflammatory cells are inherently present together during inflammation."

Applicants respectfully suggest that the Examiner's underlying basis for making this rejection is misguided. Applicants submit that it is known by persons skilled in the art that any inflammatory cells that are present in inflamed tissue caused by a disease would be present in the sub-mucosal tissue and not in the epithelium that contains the epithelial goblet cells that secrete the mucus. (See Attachment E Robbins and Cotran Pathologic Basis of Disease, page on 727, Figure 15-12) The attached figure shows the goblet cells in the epithelium and the inflammatory cells, including neutrophils and macrophages, are predominantly seen in the submucosa, and these do not contact the epithelial cells. Further, the claims of the '020 application are directed to treating mucus hypersecretion by inhibiting mucus hypersecretion by a mucus-secreting epithelial cell contained within the airway and the claims of the present application are directed to treating

inflammation by inhibiting the release of inflammatory mediators from inflammatory cells in the tissue. The separate biological functions of inflammatory cells and of mucin epithelial goblet cells do not suggest to one skilled in the art at the time the present application was filed that treatment of one type of cell to inhibit mucus hypersecretion would inhibit the release of inflammatory mediators from infiltrating inflammatory cells. In fact, a person skilled in the art would have recognized that these are separate mechanisms of biological action rather than a common mechanism to link the diverse function of these two classes of cells. Indeed, as taught by Adler, even for mucin cells, common signaling pathways and intracellular molecules involved in mucin secretion had not yet been elucidated, let alone common signaling pathways and intracellular molecules involved in both inflammation mechanisms and mucin release. The two separate and different biological functions do not suggest to one skilled in the art that a common mechanism or common mediator would interact with each cell type. Thus, there is no basis to support an obviousness-type double patenting rejection, and it is requested that this rejection be withdrawn against the pending set of claims. Additionally, the claims of the '020 application have not yet issued, and therefore, the specific language of these claims are not finalized to allow the Examiner to make a determination that the presently pending claims are obvious over those of the pending claims of the '020 application.

B. Claims 63, 75 and 84

Claims 63, 75 and 84 are rejected on the ground of obviousness-type double patenting over the '020 application in combination with the '779 patent discussed above. For the same reasons as argued above, and because the '779 patent does not cure the defects of the '020 application, applicants respectfully request reconsideration and withdrawal of this rejection to present claims 63 and 75. Claim 84 has been canceled, and therefore this rejection as applied by the Examiner to claim 84 is now moot.

CONCLUSION

In view of the remarks presented herein, Applicants respectfully submit that the claims define patentable subject matter. If, in the opinion of the Examiner, a telephonic conference would expedite the examination of this matter, the Examiner is invited to call the undersigned attorney at (919) 854-1400.

It is not believed that an extension of time and/or additional fee(s)-including fees for net addition of claims-are required, beyond those that may otherwise be provided for in documents accompanying this paper. In the event, however, that an extension of time is necessary to allow consideration of this paper, such an extension is hereby petitioned under 37 C.F.R. §1.136(a). Any additional fees believed to be due in connection with this paper may be charged to our Deposit Account No. 50-0220.

Respectfully submitted,

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Amelia Tauchen